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P01/7700 02/00-0324269.0**Request for grant of a patent**

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1. Your reference

RJW/CP6187777

2. Patent application number

(The Patent Office will fill this part in)

16 OCT 2003

0324269.0

3. Full name, address and postcode of the or of each applicant (underline all surnames)

 PHARMAGENE LABORATORIES LIMITED
 2 Orchard Road
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 HERTFORDSHIRE
 SG8 5HD

Patents ADP number (if you know it)

728S1S8002

If the applicant is a corporate body, give the country/state of its incorporation

England

4. Title of the invention

EP4 RECEPTOR ANTAGONISTS

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

 MEWBURN ELLIS
 York House
 23 Kingsway
 London WC2B 6HP

Patents ADP number (if you know it)

109006

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country

Priority application number
(if you know it)Date of filing
(day / month / year)

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Number of earlier UK application
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8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

Yes

Answer YES if:

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- b) there is an inventor who is not named as an applicant, or
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Otherwise answer NO (See note d)

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form

Description	59	/
Claim(s)	3	/
Abstract	0	<i>YMM</i>
Drawing(s)	0	

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for a preliminary examination and search (Patents Form 9/77)

1
4

Request for a substantive examination (Patents Form 10/77)

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature(s)

Mark Clark

Date 16 October 2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

ROBERT WATSON
020 7240 4405

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EP₄ RECEPTOR ANTAGONISTS

This invention relates to EP₄ receptor antagonists, pharmaceutical compositions comprising such compounds, and
5 the use of such compounds and compositions to treat various diseases.

Background to the invention

Prostanoids comprise prostaglandins (PGs) and thromboxanes
10 (Txs) and their receptors fall into five different classes (DP, EP, FP, IP and TP) based on their sensitivity to the five naturally occurring prostanoids, PGD₂, PGE₂, PGF_{2α}, PGI₂ and TXA₂, respectively (Coleman, R.A., Prostanoid Receptors.
IUPHAR compendium of receptor characterisation and
15 classification, 2nd edition, 338-353, ISBN 0-9533510-3-3, 2000). EP receptors (for which the endogenous ligand is PGE₂) have been subdivided into four types termed EP₁, EP₂, EP₃ and EP₄. These four types of EP receptors have been cloned and are distinct at both a molecular and
20 pharmacological level (Coleman, R.A., 2000)

EP₄ antagonists have been shown to be useful in the treatment of pain, and in particular, in the treatment of primary headache disorders, which include migraines, and
25 secondary headache disorders, such as drug-induced headaches (WO 00/18405 and WO 01/72302). Dilation of the cerebral vasculature and the subsequent stimulation of pain stimulating, perivascular trigeminal sensory afferent nerves is recognised to play an important role in the
30 pathophysiology of migraine. A sterile inflammatory response, associated with activation of cyclooxygenase and the generation of PGE₂, is also implicated in the pathophysiology of migraine. PGE₂ levels have been shown to be raised during migraine attacks and PGE₂ contributes to

the pain of migraine by directly dilating cerebral arteries and by stimulating the release of vasoactive/pro-inflammatory peptides from the trigeminal nerves. These effects of PGE₂ are mediated in whole or in part by EP₄ receptors. Thus, by binding to and preventing the stimulation of EP₄ receptors, EP₄ antagonists may be used to treat the pain of migraine.

EP₄ antagonists may also be useful in treating a number of other conditions and diseases. For example, they may be used in:

- the treatment of pain associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis;
- the treatment of musculoskeletal pain, lower back and neck pain, sprains and strains, neuropathic pain, sympathetically mediated pain, myositis, pain associated with cancer and fibromyalgia, pain associated with influenza or other viral infections, such as the common cold, rheumatic fever; pain associated with bowel disorders such as non-ulcer dyspepsia, irritable bowel syndrome; non-cardiac chest pain, pain associated with myocardial ischaemia, post-operative pain, headache, toothache and dysmenorrhoea. Neuropathic pain syndromes include diabetic neuropathy, sciatica, non-specific lower back pain, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, post-herpetic neuralgia, trigeminal neuralgia and pain resulting from physical trauma;
- the treatment of inflammatory diseases including rheumatoid and osteoarthritis, psoriasis, dermatitis, retinitis, conjunctivitis, asthma, bronchitis, chronic obstructive pulmonary disease, inflammatory bowel disease, colitis, nephritis, gingivitis and hepatitis;
- the treatment of cancers including familial adenomatous

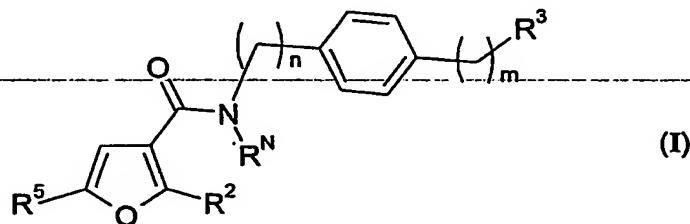
- polyposis, endometrial carcinoma, colorectal and cervical cancer;
- the treatment of bone disorders involving altered bone formation or resorption such as osteoporosis;
- 5 women's health for the treatment of myometrial and endometrial disorders;
- the treatment of gastrointestinal disease including diarrhoea;
- the treatment of immunological disorders such as autoimmune
- 10 disease, immunological deficiency diseases, organ transplantation and increasing the latency of HIV infection;
- the treatment of diseases of abnormal platelet function.
(e.g. occlusive vascular diseases);
- the preparation of a drug with diuretic properties to treat
- 15 or prevent various oedema, hypertension, premenstrual tension, urinary calculus, oliguria, hyperphosphaturia, mesangial proliferative glomerulonephritis, chronic renal failure or the like;
- the treatment of impotence or erectile dysfunction, and
- 20 female sexual dysfunction;
- the treatment of hair growth disorders;
- the treatment of sleep disorders such as narcolepsy and insomnia;
- the treatment of cardiovascular diseases and shock states
- 25 associated with hypotension (e.g. septic shock);
- the treatment of neurodegenerative diseases and for preventing neuronal damage following stroke, cardiac arrest, cardiopulmonary bypass, traumatic brain injury or spinal cord injury;
- 30 the treatment of tinnitus;
- the treatment of dependence; and
- the treatment of complications of diabetes.

Although EP₄ antagonists are known, it is desired to find

novel EP₄ antagonists, and in particular, EP₄ antagonists which are selective against other EP receptors, i.e. EP₁, EP₂ and EP₃.

5 *Summary of the invention*

A first aspect of the present invention provides a compound of formula (I):



or a salt, solvate and chemically protected form thereof,
10 wherein:

one of R² and R⁵ is:

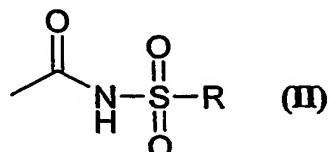
- (i) H or an optionally substituted C₁₋₄ alkyl group; or
- (ii) an optionally substituted C₅₋₇ aryl; and the other of R² and R⁵ is the other group;

15 m and n can be 0 or 1, and m + n = 1 or 2

R^N is H or optionally substituted C₁₋₄ alkyl

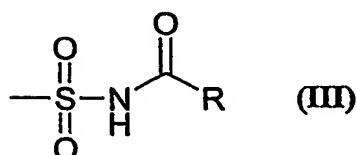
R³ is either:

- (i) carboxy;
- (ii) a group of formula (II):



20 ;

- (iii) a group of formula (III):



wherein R is optionally substituted C₁₋₇ alkyl, C₅₋₂₀ aryl, or NR^{N3}R^{N4}, where R^{N3} and R^{N4} are independently selected from

optionally substituted C₁₋₄ alkyl; or
(iv) tetrazol-5-yl.

A second aspect of the present invention provides a compound
5 of formula (I) or a pharmaceutically acceptable salt thereof
for use in a method of therapy.

A third aspect of the present invention provides a pharmaceutical composition comprising a compound of formula
10 (I) as defined in the first aspect or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

A further aspect of the present invention provides the use
15 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by antagonism of an EP₄ receptor.

20 Another aspect of the present invention provides a method of treating a condition which can be alleviated by antagonism of an EP₄ receptor, which method comprises administering to a patient in need of treatment an effective amount of a compound of formula (I), or a pharmaceutically acceptable
25 salt thereof.

Conditions which can be alleviated by antagonism of an EP₄ receptor are discussed above, and particularly include primary headache disorders, most particularly migraines.

30 The present invention also provides methods of antagonizing EP₄ receptors, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound of formula (I).

In some embodiments, the compounds described above may be selective as against antagonism of the other three EP receptors, i.e. EP₁, EP₂ and EP₃. This selectivity allows for targeting of the effect of the compounds of the invention, with possible benefits in the treatment of certain conditions.

Definitions

Monodentate groups

10 (i.e groups with one point of covalent attachment)

Alkyl: The term "alkyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 7 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated or unsaturated. Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cylcoalkynyl, etc., discussed below.

20

In the context of alkyl groups, the prefixes (e.g. C₁₋₄, C₁₋₇) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C₁₋₄ alkyl" as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C₁₋₄ alkyl ("lower alkyl") and C₁₋₇ alkyl. Note that the first prefix may vary according to other limitations; for example, for unsaturated alkyl groups, the first prefix must be at least 2; for cyclic alkyl groups, the first prefix must be at least 3; etc.

Examples of saturated alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), propyl (C₃), butyl (C₄), pentyl (C₅), hexyl (C₆) and heptyl (C₇).

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (amyl) (C_5), n-hexyl (C_6), and n-
5 heptyl (C_7).

Examples of saturated branched alkyl groups include iso-propyl (C_3), iso-butyl (C_4), sec-butyl (C_4), tert-butyl (C_4), iso-pentyl (C_5), and neo-pentyl (C_5).

10

Alkenyl: The term "alkenyl" as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds.

Examples of alkenyl groups include C_{2-4} alkenyl and C_{2-7} alkenyl. Examples of alkenyl groups include, but are not

15 limited to, ethenyl (vinyl, $-CH=CH_2$), 1-propenyl ($-CH=CH-$ CH₃), 2-propenyl (allyl, $-CH-CH=CH_2$), isopropenyl (1-methylvinyl, $-C(CH_3)=CH_2$), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

20 Alkynyl: The term "alkynyl" as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds. Examples of groups of alkynyl groups include C_{2-4} alkynyl and C_{2-7} alkynyl. Examples of alkynyl groups include, but are not limited to, ethynyl (ethinyl, $-C\equiv CH$) and 2-propynyl
25 (propargyl, $-CH_2-C\equiv CH$).

30 Cycloalkyl: The term "cycloalkyl" as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a carbocyclic ring of a carbocyclic compound, which carbocyclic ring may be saturated or unsaturated, which moiety has from 3 to 7 carbon atoms (unless otherwise specified), including from 3 to 7 ring atoms. Thus, the term "cycloalkyl" includes the

sub-classes cycloalkenyl and cycloalkynyl. Preferably, each ring has from 3 to 7 ring atoms. Examples of groups of cycloalkyl groups include C₃₋₇ cycloalkyl.

- 5 Examples of cycloalkyl groups include, but are not limited to, those derived from:

saturated monocyclic hydrocarbon compounds:

cyclopropane (C₃), cyclobutane (C₄), cyclopentane (C₅), cyclohexane (C₆), cycloheptane (C₇), methylcyclopropane (C₄),
10 dimethylcyclopropane (C₅), methylcyclobutane (C₅), dimethylcyclobutane (C₆), methylcyclopentane (C₆), dimethylcyclopentane (C₇), methylcyclohexane (C₇);

unsaturated monocyclic hydrocarbon compounds:

cyclopropene (C₃), cyclobutene (C₄), cyclopentene (C₅), cyclohexene (C₆), methylcyclopropene (C₄), dimethylcyclopropene (C₅), methylcyclobutene (C₅), dimethylcyclobutene (C₆), methylcyclopentene (C₆), dimethylcyclopentene (C₇), methylcyclohexene (C₇);

- 20 Heterocyclyl: The term "heterocyclyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms.

- 25 Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

In this context, the prefixes (e.g. C₃₋₂₀, C₃₋₇, C₅₋₆, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C₅₋₆ heterocyclyl" as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C₃₋₂₀ heterocyclyl, C₅₋₂₀ heterocyclyl, C₃₋₁₅ heterocyclyl, C₅₋₁₅ heterocyclyl, C₃₋₁₂

heterocyclyl, C₅₋₁₂ heterocyclyl, C₃₋₁₀ heterocyclyl, C₅₋₁₀ heterocyclyl, C₃₋₇ heterocyclyl, C₅₋₇ heterocyclyl, and C₅₋₆ heterocyclyl.

5 Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N₁: aziridine (C₃), azetidine (C₄), pyrrolidine (tetrahydropyrrole) (C₅), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C₅), 2H-pyrrole or 3H-pyrrole

10 (isopyrrole, isoazole) (C₅), piperidine (C₆), dihydropyridine (C₆), tetrahydropyridine (C₆), azepine (C₇);

O₁: oxirane (C₃), oxetane (C₄), oxolane (tetrahydrofuran) (C₅), oxole (dihydrofuran) (C₅), oxane (tetrahydropyran) (C₆), dihydropyran (C₆), pyran (C₆), oxepin (C₇);

15 S₁: thiirane (C₃), thietane (C₄), thiolane (tetrahydrothiophene) (C₅), thiane (tetrahydrothiopyran) (C₆), thiepane (C₇);

O₂: dioxolane (C₅), dioxane (C₆), and dioxepane (C₇);

O₃: trioxane (C₆);

20 N₂: imidazolidine (C₅), pyrazolidine (diazolidine) (C₅), imidazoline (C₅), pyrazoline (dihydropyrazole) (C₅), piperazine (C₆);

N₁O₁: tetrahydrooxazole (C₅), dihydrooxazole (C₅), tetrahydroisoxazole (C₅), dihydroisoxazole (C₅), morpholine (C₆), tetrahydrooxazine (C₆), dihydrooxazine (C₆), oxazine (C₆);

N₁S₁: thiazoline (C₅), thiazolidine (C₅),

thiomorpholine (C₆);

N₂O₁: oxadiazine (C₆);

30 O₁S₁: oxathiole (C₅) and oxathiane (thioxane) (C₆); and, N₁O₁S₁: oxathiazine (C₆).

Aryl: The term "aryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from

an aromatic ring atom of an aromatic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 5 to 7 ring atoms.

- 5 In this context, the prefixes (e.g. C₃₋₂₀, C₅₋₇, C₅₋₆, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C₅₋₆ aryl" as used herein, pertains to an aryl group having 5 or 6 ring atoms. Examples of groups of aryl groups include C₃₋₂₀ aryl, C₅₋₂₀ aryl, C₅₋₁₅ aryl, C₅₋₁₂ aryl, C₅₋₁₀ aryl, C₅₋₇ aryl, C₅₋₆ aryl, C₅ aryl, and C₆ aryl.

The ring atoms may be all carbon atoms, as in "carboaryl groups". Examples of carboaryl groups include C₃₋₂₀ carboaryl, C₅₋₂₀ carboaryl, C₅₋₁₅ carboaryl, C₅₋₁₂ carboaryl, C₅₋₁₀ carboaryl, C₅₋₇ carboaryl, C₅₋₆ carboaryl, C₅ carboaryl, and C₆ carboaryl.

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e. phenyl) (C₆), naphthalene (C₁₀), azulene (C₁₀), anthracene (C₁₄), phenanthrene (C₁₄), naphthacene (C₁₈), and pyrene (C₁₆).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indane (e.g., 2,3-dihydro-1H-indene) (C₉), indene (C₉), isoindene (C₉), tetrалine (1,2,3,4-tetrahydronaphthalene (C₁₀), acenaphthene (C₁₂), fluorene (C₁₃), phenalene (C₁₃), acephenanthrene (C₁₅), and 30 aceanthrene (C₁₆).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups". Examples of heteroaryl groups include C₃₋₂₀ heteroaryl, C₅₋₂₀ heteroaryl,

C₅₋₁₅ heteroaryl, C₅₋₁₂ heteroaryl, C₅₋₁₀ heteroaryl, C₅₋₇ heteroaryl, C₅₋₆ heteroaryl, C₅ heteroaryl, and C₆ heteroaryl.

Examples of monocyclic heteroaryl groups include, but are
5 not limited to, those derived from:

- N₁: pyrrole (azole) (C₅), pyridine (azine) (C₆);
O₁: furan (oxole) (C₅);
S₁: thiophene (thiole) (C₅);
N₁O₁: oxazole (C₅), isoxazole (C₅), isoxazine (C₆);
10 N₂O₁: oxadiazole (furazan) (C₅);
N₃O₁: oxatriazole (C₅);
N₁S₁: thiazole (C₅), isothiazole (C₅);
N₂: imidazole (1,3-diazole) (C₅), pyrazole
(1,2-diazole) (C₅), pyridazine (1,2-diazine) (C₆),
15 pyrimidine (1,3-diazine) (C₆), pyrazine (1,4-diazine) (C₆);
N₃: triazole (C₅), triazine (C₆); and,
N₄: tetrazole (C₅).

Examples of heteroaryl groups which comprise fused rings,
20 include, but are not limited to:

- C₉ (with 2 fused rings) derived from benzofuran (O₁),
isobenzofuran (O₁), indole (N₁), isoindole (N₁), indolizine
(N₁), indoline (N₁), isoindoline (N₁), purine (N₄) (e.g.,
adenine, guanine), benzimidazole (N₂), indazole (N₂),
25 benzoxazole (N₁O₁), benzisoxazole (N₁O₁), benzodioxole (O₂),
benzofurazan (N₂O₁), benzotriazole (N₃), benzothiofuran (S₁),
benzothiazole (N₁S₁), benzothiadiazole (N₂S);
C₁₀ (with 2 fused rings) derived from chromene (O₁),
isochromene (O₁), chroman (O₁), isochroman (O₁), benzodioxan
30 (O₂), quinoline (N₁), isoquinoline (N₁), quinolizine (N₁),
benzoxazine (N₁O₁), benzodiazine (N₂), pyridopyridine (N₂),
quinoxaline (N₂), quinazoline (N₂), cinnoline (N₂),
phthalazine (N₂), naphthyridine (N₂), pteridine (N₄);

C₁₁ (with 2 fused rings) derived from benzodiazepine (N₂);

C₁₃ (with 3 fused rings) derived from carbazole (N₁), dibenzofuran (O₁), dibenzothiophene (S₁), carboline (N₂),
5 perimidine (N₂), pyridoindole (N₂); and,

C₁₄ (with 3 fused rings) derived from acridine (N₁), xanthene (O₁), thioxanthene (S₁), oxanthrene (O₂), phenoxathiin (O₁S₁), phenazine (N₂), phenoxazine (N₁O₁), phenothiazine (N₁S₁), thianthrene (S₂), phenanthridine (N₁),
10 phenanthroline (N₂), phenazine (N₂).

If a heteroaryl or heterocyclyl group contains a nitrogen ring atom, this ring atom, where possible, may be in a oxidised state, as an N-oxide.

15

The above groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves, the additional monodentate substituents listed below and alkoxylenes.

20

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

25 Ether: -OR, wherein R is an ether substituent, for example, a C₁₋₇ alkyl group (also referred to as a C₁₋₇ alkoxy group, discussed below), a C₃₋₂₀ heterocyclyl group (also referred to as a C₃₋₂₀ heteroclyloxy group), or a C₅₋₂₀ aryl group (also referred to as a C₅₋₂₀ aryloxy group), preferably a C₁₋₇ alkyl group.
30

C₁₋₇ alkoxy: -OR, wherein R is a C₁₋₇ alkyl group. Examples of C₁₋₇ alkoxy groups include, but are not limited to, -OMe (methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr)

(isopropoxy), $-O(nBu)$ (n-butoxy), $-O(sBu)$ (sec-butoxy),
 $-O(iBu)$ (isobutoxy), and $-O(tBu)$ (tert-butoxy).

Oxo (keto, -one): $=O$.

5

Thione (thioketone): $=S$.

Imino (imine): $=NR$, wherein R is an imino substituent, for example, hydrogen, C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl 10 group, or a C₅₋₂₀ aryl group, preferably hydrogen or a C₁₋₇ alkyl group. Examples of imino groups include, but are not limited to, $=NH$, $=NMe$, $=NET$, and $=NPh$.

Formyl (carbaldehyde, carboxaldehyde): $-C(=O)H$.

15

Acyl (keto): $-C(=O)R$, wherein R is an acyl substituent, for example, a C₁₋₇ alkyl group (also referred to as C₁₋₇ alkylacyl or C₁₋₇ alkanoyl), a C₃₋₂₀ heterocyclyl group (also referred to as C₃₋₂₀ heterocyclacyl), or a C₅₋₂₀ aryl group 20 (also referred to as C₅₋₂₀ arylacyl), preferably a C₁₋₇ alkyl group. Examples of acyl groups include, but are not limited to, $-C(=O)CH_3$ (acetyl); $-C(=O)CH_2CH_3$ (propionyl), $-C(=O)C(CH_3)_3$ (t-butyryl), and $-C(=O)Ph$ (benzoyl, phenone).

25 Carboxy (carboxylic acid): $-C(=O)OH$.

Thiocarboxy (thiocarboxylic acid): $-C(=S)SH$.

Thiolocarboxy (thiolocarboxylic acid): $-C(=O)SH$.

30

Thionocarboxy (thionocarboxylic acid): $-C(=S)OH$.

Imidic acid: $-C(=NH)OH$.

Hydroxamic acid: $-\text{C}(=\text{NOH})\text{OH}$.

Ester (carboxylate, carboxylic acid ester, oxycarbonyl):

$-\text{C}(=\text{O})\text{OR}$, wherein R is an ester substituent; for example, a

5 C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, $-\text{C}(=\text{O})\text{OCH}_3$,

$-\text{C}(=\text{O})\text{OCH}_2\text{CH}_3$, $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$, and $-\text{C}(=\text{O})\text{OPh}$.

10 Acyloxy (reverse ester): $-\text{OC}(=\text{O})\text{R}$, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of acyloxy groups include, but are not limited to, $-\text{OC}(=\text{O})\text{CH}_3$ (acetoxy), $-\text{OC}(=\text{O})\text{CH}_2\text{CH}_3$,

15 $-\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$, $-\text{OC}(=\text{O})\text{Ph}$, and $-\text{OC}(=\text{O})\text{CH}_2\text{Ph}$.

Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide):

$-\text{C}(=\text{O})\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino

substituents, as defined for amino groups. Examples of

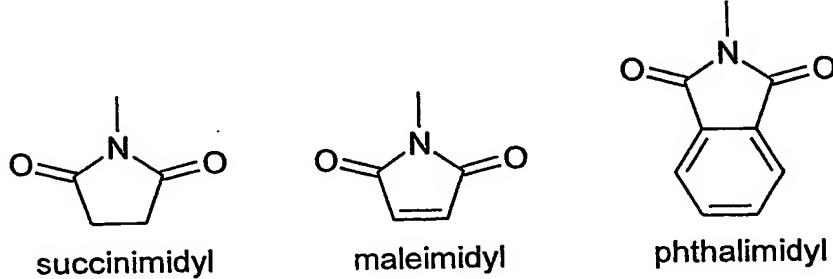
20 amido groups include, but are not limited to, $-\text{C}(=\text{O})\text{NH}_2$,
 $-\text{C}(=\text{O})\text{NHCH}_3$, $-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, $-\text{C}(=\text{O})\text{NHCH}_2\text{CH}_3$, and
 $-\text{C}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, as well as amido groups in which R^1 and R^2 , together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example,

25 piperidinocarbonyl, morpholinocarbonyl,
thiomorpholinocarbonyl, and piperazinocarbonyl.

Acylamino: $-\text{NR}^1\text{C}(=\text{O})\text{R}^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl

30 group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group, and R^2 is an acyl substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group. Examples of acylamide groups include, but are not limited to,

$-\text{NHC}(=\text{O})\text{CH}_3$, $-\text{NHC}(=\text{O})\text{CH}_2\text{CH}_3$, and $-\text{NHC}(=\text{O})\text{Ph}$. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:



5

Thioamido (thiocarbamyl): $-\text{C}(=\text{S})\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of thioamido groups include, but are not limited to, $-\text{C}(=\text{S})\text{NH}_2$, $-\text{C}(=\text{S})\text{NHCH}_3$, $-\text{C}(=\text{S})\text{N}(\text{CH}_3)_2$, and

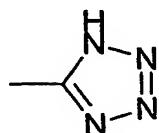
10 $-\text{C}(=\text{S})\text{NHCH}_2\text{CH}_3$.

Ureido: $-\text{N}(\text{R}^1)\text{CONR}^2\text{R}^3$ wherein R^2 and R^3 are independently amino substituents, as defined for amino groups, and R^1 is a ureido substituent, for example, hydrogen, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably hydrogen or a C₁₋₇ alkyl group. Examples of ureido groups include, but are not limited to, $-\text{NHCONH}_2$, $-\text{NHCONHMe}$, $-\text{NHCONHET}$, $-\text{NHCONMe}_2$, $-\text{NHCONET}_2$, $-\text{NMeCONH}_2$, $-\text{NMeCONHMe}$, $-\text{NMeCONHET}$, $-\text{NMeCONMe}_2$, and $-\text{NMeCONET}_2$.

20

Guanidino: $-\text{NH}-\text{C}(=\text{NH})\text{NH}_2$.

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



25

Amino: $-\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylamino or di- C_{1-7} alkylamino), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a
5 C_{1-7} alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2 , taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary ($-\text{NH}_2$), secondary ($-\text{NHR}^1$), or tertiary ($-\text{NHR}^1\text{R}^2$), and in cationic form, may be
10 quaternary ($-\text{NR}^1\text{R}^2\text{R}^3$). Examples of amino groups include, but are not limited to, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHC}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$, and $-\text{NHPH}$. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and
15 thiomorpholino.

Amidine (amidino): $-\text{C}(=\text{NR})\text{NR}_2$, wherein each R is an amidine substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H
20 or a C_{1-7} alkyl group. Examples of amidine groups include, but are not limited to, $-\text{C}(=\text{NH})\text{NH}_2$, $-\text{C}(=\text{NH})\text{NMe}_2$, and $-\text{C}(=\text{NMe})\text{NMe}_2$.

Nitro: $-\text{NO}_2$.

25

Nitroso: $-\text{NO}$.

Cyano (nitrile, carbonitrile): $-\text{CN}$.

30 Sulfhydryl (thiol, mercapto): $-\text{SH}$.

Thioether (sulfide): $-\text{SR}$, wherein R is a thioether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7} alkylthio group), a C_{3-20} heterocyclyl group, or a

C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of C_{1-7} alkylthio groups include, but are not limited to, $-SCH_3$ and $-SCH_2CH_3$.

5 Disulfide: $-SS-R$, wherein R is a disulfide substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group (also referred to herein as C_{1-7} alkyl disulfide). Examples of C_{1-7} alkyl disulfide groups include, but are not limited to, $-SSCH_3$ and
10 $-SSCH_2CH_3$.

Sulfine (sulfinyl, sulfoxide): $-S(=O)R$, wherein R is a sulfine substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfine groups include, but are
15 not limited to, $-S(=O)CH_3$ and $-S(=O)CH_2CH_3$.

Sulfone (sulfonyl): $-S(=O)_2R$, wherein R is a sulfone substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group, including, for example, a fluorinated or perfluorinated C_{1-7} alkyl group. Examples of sulfone groups include, but are not limited to, $-S(=O)_2CH_3$ (methanesulfonyl, mesyl), $-S(=O)_2CF_3$ (triflyl), $-S(=O)_2CH_2CH_3$ (esyl), $-S(=O)_2C_4F_9$ (nonaflyl), $-S(=O)_2CH_2CF_3$ (tresyl), $-S(=O)_2CH_2CH_2NH_2$ (tauryl), $-S(=O)_2Ph$ (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl (closyl), 4-bromophenylsulfonyl (brosyl), 4-nitrophenyl (nosyl), 2-naphthalenesulfonate (napsyl), and
25 30 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

Sulfinic acid (sulfino): $-S(=O)OH$, $-SO_2H$.

Sulfonic acid (sulfo): $-S(=O)_2OH$, $-SO_3H$.

Sulfinate (sulfinic acid ester): $-S(=O)OR$; wherein R is a sulfinate substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group. Examples of sulfinate groups include, but are not limited to, $-S(=O)OCH_3$ (methoxysulfinyl; methyl sulfinate) and $-S(=O)OCH_2CH_3$ (ethoxysulfinyl; ethyl sulfinate).

10 Sulfinyloxy: $-OS(=O)R$, wherein R is a sulfinyloxy substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group. Examples of sulfinyloxy groups include, but are not limited to, $-OS(=O)CH_3$ and $-OS(=O)CH_2CH_3$.

15 Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide): $-S(=O)NR^1R^2$, wherein R¹ and R² are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-S(=O)NH_2$,
20 $-S(=O)NH(CH_3)$, $-S(=O)N(CH_3)_2$, $-S(=O)NH(CH_2CH_3)$,
 $-S(=O)N(CH_2CH_3)_2$, and $-S(=O)NHPH$.

25 Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide): $-S(=O)_2NR^1R^2$, wherein R¹ and R² are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to,
 $-S(=O)_2NH_2$, $-S(=O)_2NH(CH_3)$, $-S(=O)_2N(CH_3)_2$, $-S(=O)_2NH(CH_2CH_3)$,
 $-S(=O)_2N(CH_2CH_3)_2$, and $-S(=O)_2NHPH$.

30 Sulfonamino: $-NR^1S(=O)_2R$, wherein R¹ is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇

alkyl group. Examples of sulfonamino groups include, but are not limited to, $-\text{NHS}(\text{=O})_2\text{CH}_3$ and $-\text{N}(\text{CH}_3)\text{S}(\text{=O})_2\text{C}_6\text{H}_5$.

Sulfinamino: $-\text{NR}^1\text{S}(\text{=O})\text{R}$, wherein R^1 is an amino substituent,
5 as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinamino groups include, but are not limited to, $-\text{NHS}(\text{=O})\text{CH}_3$ and $-\text{N}(\text{CH}_3)\text{S}(\text{=O})\text{C}_6\text{H}_5$.

10

As already mentioned, the above described groups may be substituted, and particular examples include, but are not limited to, C_{3-20} aryl- C_{1-7} alkyl groups, which include benzyl (phenylmethyl, PhCH_2-), benzhydryl ($\text{Ph}_2\text{CH}-$), trityl (triphenylmethyl, $\text{Ph}_3\text{C}-$), phenethyl (phenylethyl, $\text{Ph-CH}_2\text{CH}_2-$), styryl (Ph-CH=CH-) and cinnamyl (Ph-CH=CH-CH_2-).

Bidentate groups

(i.e. groups with two points of covalent attachment; linking
20 groups)

Alkylene: The term "C₁₋₃ alkylene", as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms from each of two different carbon atoms, of a linear hydrocarbon compound having from 1 to 3 carbon atoms, which
25 may be saturated or unsaturated. Thus, the term "alkylene" includes the sub-classes alkenylene and alkynylene.

In this context, the prefix C₁₋₃ denotes the number of carbon atoms, or range of number of carbon atoms.

30

Examples of saturated C₁₋₃ alkylene groups include $-\text{CH}_2-$ (methylene), $-\text{CH}_2\text{CH}_2-$ (ethylene) and $-\text{CH}_2\text{CH}_2\text{CH}_2-$ (propylene).

Examples of unsaturated C₁₋₃ alkylene groups (which may be termed "C₂₋₃ alkenylene" or "C₂₋₃ alkynylene", as appropriate) include -CH=CH- (vinylene), -CH=CH-CH₂-, -CH₂-CH=CH-, -C≡C-, -C≡C-CH₂- and -CH₂-C≡C-.

5

The C₁₋₃ alkylene group may be substituted by any monodentate substituent described above.

Alkoxylenes: The term "alkoxylenes," as used herein, pertains

10 to a bidentate group of formula -O(CH₂)_nO-, where n is 1 or 2.

Includes Other Forms

Unless otherwise specified, included in the above are the

15 well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form (-COO⁻), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group 20 includes the protonated form (-N⁺HR¹R²), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group.

Similarly, a reference to a hydroxyl group also includes the 25 anionic form (-O⁻), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

Isomers, Salts, Solvates and Protected Forms

Certain compounds may exist in one or more particular

geometric, optical, enantiomeric, diastereomeric, epimeric,

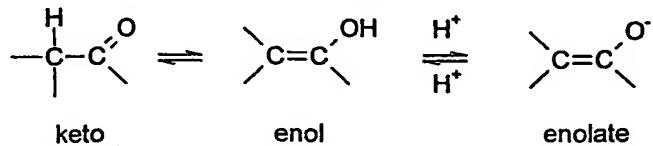
30 stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and

anti-forms; synclinal- and anticlinal-forms; α - and β -forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or 5 "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers", as used herein, are structural (or constitutional) isomers

10 (i.e. isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-\text{OCH}_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-\text{CH}_2\text{OH}$. Similarly, a reference to 15 ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g. C_1 -alkyl includes n-propyl and iso-propyl; butyl 20 includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for 25 example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For

example, H may be in any isotopic form, including ^1H , ^2H (D), and ^3H (T); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; and the like.

5

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g. asymmetric synthesis) and separation (e.g. fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

10

15

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

20

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge, et al., *J. Pharm. Sci.*, 66, 1-19 (1977).

25

30

For example, if the compound is anionic, or has a functional group which may be anionic (e.g. $-\text{COOH}$ may be $-\text{COO}^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+ , alkaline earth cations such as Ca^{2+} and Mg^{2+} , and other cations such as Al^{3+} . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e. NH_4^+) and substituted ammonium ions (e.g. NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+). Examples of some suitable substituted ammonium ions are those derived

from: ethylamine, diethylamine, dicyclohexylamine,
triethylamine, butylamine, ethylenediamine, ethanolamine,
diethanolamine, piperazine, benzylamine, phenylbenzylamine,
choline, meglumine, and tromethamine, as well as amino
5 acids, such as lysine and arginine. An example of a common
quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

If the compound is cationic, or has a functional group which
may be cationic (e.g. $-\text{NH}_2$ may be $-\text{NH}_3^+$), then a salt may be
10 formed with a suitable anion. Examples of suitable
inorganic anions include, but are not limited to, those
derived from the following inorganic acids: hydrochloric,
hydrobromic, hydroiodic, sulfuric, sulfurous, nitric,
nitrous, phosphoric, and phosphorous.

15 Examples of suitable organic anions include, but are not
limited to, those derived from the following organic acids:
2-acethoxybenzoic, acetic, ascorbic, aspartic, benzoic,
camphorsulfonic, cinnamic, citric, edetic, ethanesulfonic,
20 ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic,
glycolic, hydroxymaleic, hydroxynaphthalene carboxylic,
isethionic, lactic, lactobionic, lauric, maleic, malic,
methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic,
pantothenic, phenylacetic, phenylsulfonic, propionic,
25 pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric,
toluenesulfonic, and valeric. Examples of suitable
polymeric organic anions include, but are not limited to,
those derived from the following polymeric acids: tannic
acid, carboxymethyl cellulose.

30 It may be convenient or desirable to prepare, purify, and/or
handle a corresponding solvate of the active compound. The
term "solvate" is used herein in the conventional sense to
refer to a complex of solute (e.g., active compound, salt of

active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

- 5 It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected
- 10 from undesirable chemical reactions under specified conditions (e.g. pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified
- 15 conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without
- 20 affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).
- 25

A wide variety of such "protecting", "blocking", or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a

reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

5

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or

10 t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH(OR)₂) or ketal (R₂C(OR)₂), respectively, in
15 which the carbonyl group (>C=O) is converted to a diether (>C(OR)₂), by reaction with, for example, a primary alcohol.

The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

20

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: an acetamide (-NHCO-CH₃); a benzyloxy amide (-NHCO-OCH₂C₆H₅, -NH-Cbz); as a t-butoxy amide (-NHCO-OC(CH₃)₃,
25 -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a
2-trimethylsilylethoxy amide (-NH-Teoc), as a 2,2,2-trichloroethoxy amide (-NH-Troc), as an allyloxy amide
30 (-NH-Alloc), as a 2(-phenylsulfonyl)ethoxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O·).

For example, a carboxylic acid group may be protected as an ester for example, as: an C₁₋₇ alkyl ester (e.g., a methyl ester; a t-butyl ester); a C₁₋₇ haloalkyl ester (e.g., a C₁₋₇ trihaloalkyl ester); a triC₁₋₇ alkylsilyl-C₁₋₇ alkyl ester; or 5 a C₅₋₂₀ aryl-C₁₋₇ alkyl ester (e.g. a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether 10 (=SR); for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH₂NHC(=O)CH₃).

The term "treatment", as used herein in the context of treating a condition, pertains generally to treatment and 15 therapy, whether of a human or an animal (e.g. in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the 20 condition, and cure of the condition. Treatment as a prophylactic measure (i.e. prophylaxis) is also included.

The term "therapeutically-effective amount", as used herein, pertains to that amount of an active compound, or a 25 material, composition or dosage form comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen. Suitable dose ranges will 30 typically be in the range of from 0.01 to 20 mg/kg/day, preferably from 0.1 to 10 mg/kg/day.

Compositions and their administration

Compositions may be formulated for any suitable route and

means of administration. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including 5 subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into 10 association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, 15 if necessary, shaping the product.

For solid compositions, conventional non-toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, starch, 20 magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like may be used. The active compound as defined above may be formulated as suppositories using, for example, polyalkylene glycols, acetylated triglycerides and the like, as the carrier. 25 Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc, an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline aqueous dextrose, glycerol, ethanol, and the like, to 30 thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate,

triethanolamine sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's 5 Pharmaceutical Sciences, 20th edition, pub. Lippincott, Williams & Wilkins, 2000. The composition or formulation to be administered will, in any event, contain a quantity of the active compound(s) in an amount effective to alleviate the symptoms of the subject being treated.

10 Dosage forms or compositions containing active ingredient in the range of 0.25 to 95% with the balance made up from non-toxic carrier may be prepared.

15 For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, sodium crosscarmellose, starch, 20 magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain 25 1%-95% active ingredient, more preferably 2-50%, most preferably 5-8%.

30 Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the

like. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, triethanolamine sodium acetate, etc.

The percentage of active compound contained in such parental compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject. However, percentages of active ingredient of 0.1% to 10% in solution are employable, and will be higher if the composition is a solid which will be subsequently diluted to the above percentages. Preferably, the composition will comprise 0.2-2% of the active agent in solution.

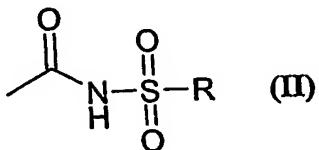
Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

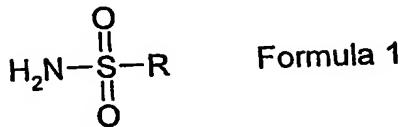
For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et₂O), acetic acid (AcOH), dichloromethane (methylene chloride, DCM), acetonitrile (ACN), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO).

General Synthesis Methods

Compounds of the invention wherein R³ is of formula (II):

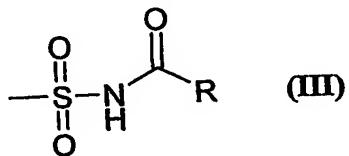


5 may be synthesised from the analogous compound of the invention wherein R³ is carboxy, by reaction with a compound of formula 1:

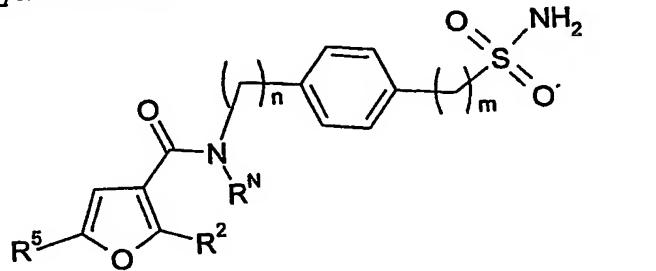


10 in basic conditions, preferably aided by a coupling agent, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

Compounds of the invention wherein R³ is of formula (III):



15 may be synthesized from a compound of formula 2:



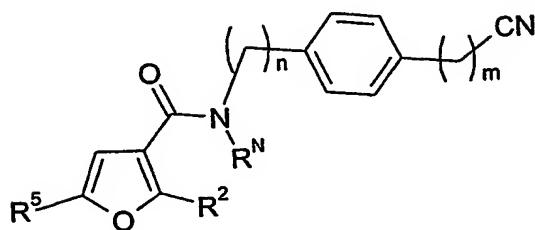
Formula 2

by reaction with a compound of formula 3:

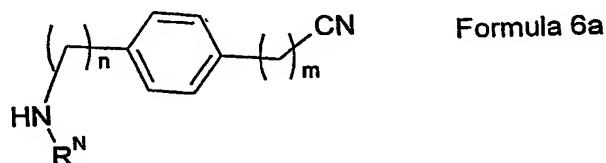
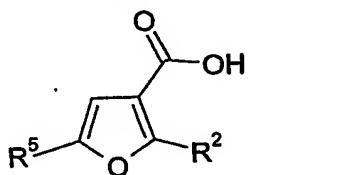


wherein X is either OH or halo, where if X is OH, the use of 20 basic conditions and a coupling agent is preferred.

Compounds where R³ is tetrazol-5-yl may be synthesised from compounds of formula 4:

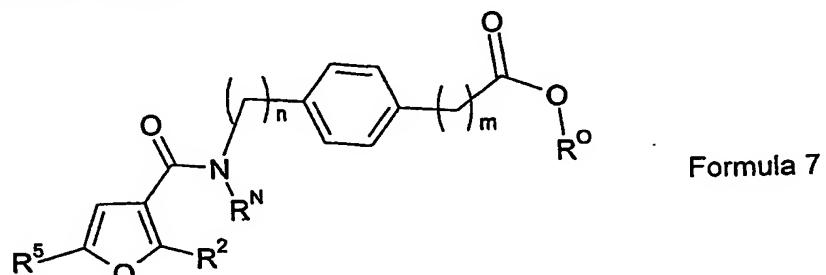


- 5 by treatment with sodium azide in the presence of a base.
Compounds of formula 4 may be synthesised by coupling compounds of Formula 5 and Formula 6a.



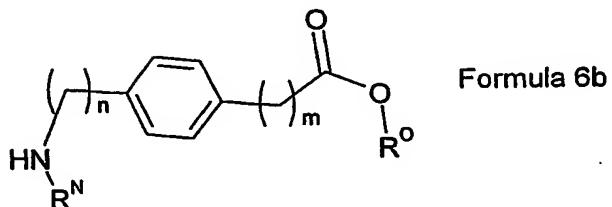
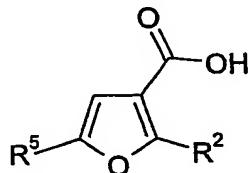
- 10 Such a coupling step may be carried out using a coupling agent, for example, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate.

Compounds where R³ is carboxy, may be synthesised from compounds of formula 7:



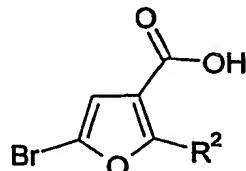
, where R⁰ is typically a C₁₋₄ alkyl group, by a hydrolysis reaction, for example, using sodium hydroxide.

Compounds of formula 7 can be synthesised by coupling 5 compounds of formula 5 and 6b:

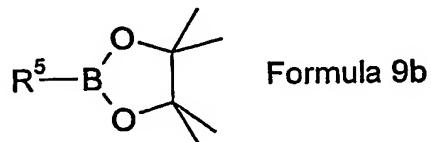
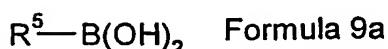


Such a coupling step may be carried out as described above, by using a coupling agent, for example, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium 10 hexafluorophosphate.

In compounds of formula 5, if R⁵ is an aryl group, then these may be synthesised from compounds of formula 8:

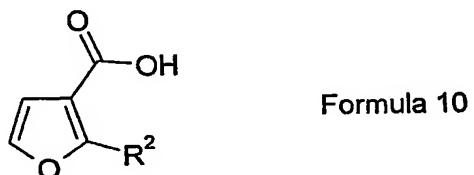


15 by a Suzuki coupling of a compound of formula 9a (or equivalent ester of formula 9b):



The Suzuki coupling may be achieved using, for example, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) as the palladium catalyst.

- 5 Compounds of Formula 8 may be synthesised from compounds of formula 10:



by treating the compound of formula 10 with a brominating agent, such as pyridinium tribromide.

- 10 Compounds where R² or R⁵ is a phenyl group substituted by -O-CHF₂, can be synthesised from the corresponding compound where the phenyl group is substituted by -OH, by treating this compound with a base and chlorodifluoromethane.

- 15 *Preferences*
The following preferences may be combined with one another, and may be different for each aspect of the present invention.

- 20 R⁵ is preferably the optionally substituted C₅₋₇ aryl group and R² is preferably H or the optionally substituted C₁₋₄ alkyl group.

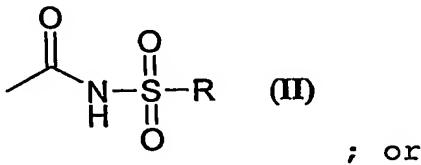
- 25 R² is preferably selected from H or an optionally substituted C₁₋₃ alkyl group, more preferably H, methyl, CF₃ or iso-propyl, and most preferably R² is a methyl group.

- 30 R⁵ is preferably a C₆ aryl group, and is more preferably phenyl. R⁵ may be substituted, and preferred substituents include C₁₋₇ alkoxy groups, more preferably C₁₋₄ alkoxy

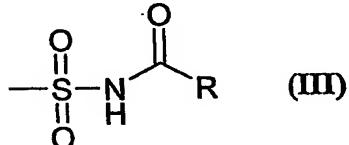
groups, e.g. -OMe, -OCF₃, -OEt, -OCHF₂, with -OCHF₂ being the most preferred.

R³ is preferably either:

- 5 (i) a group of formula (II):



- (ii) a group of formula (III):



with a group of formula (II) being more preferred. In some 10 embodiments, R³ is preferably carboxy.

Where R³ is of formula (II) or (III), R is preferably selected from an optionally substituted C₅₋₂₀ aryl group, and an optionally substituted C₅₋₂₀ aryl-C₁₋₇ alkyl group, wherein 15 the C₁₋₇ alkyl group is more preferably methyl. In these groups the C₅₋₂₀ aryl group is preferably a C₆ aryl group. Such groups may preferably be substituted with C₁₋₄ alkyl groups, such as methyl and hydroxy or halo groups, for example, fluoro. Thus, preferred R groups include, but are 20 not limited to: phenyl; benzyl; 2-fluoro-phenyl; 4-hydroxy-phenyl; 2-trifluoromethyl-phenyl; 5-methyl-pyrid-2-yl.

If R in formula (II) or (III) is a C₁₋₇ alkyl group, it is more preferably a C₁₋₄ alkyl group, for example methyl or 25 propyl.

Preferably n + m = 1, and more preferably n is 0 and m is 1.

R^N is preferably H or methyl, and is more preferably H.

Particularly preferred compounds of the present invention include:

- 5 (4-{[5-(4-Methoxy-phenyl)-2-trifluoromethyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid (4);
(4-{[5-(4-Methoxy-phenyl)-2-methyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid (6);
(4-[(5-Phenyl-furan-3-carbonyl)-amino]-phenyl)-acetic acid
10 (10);
(4-{[5-(4-Difluoromethoxy-phenyl)-furan-3-carbonyl]-amino}-phenyl)-acetic acid (13);
(4-{[5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid (18);
15 4-{[(5-Methyl-2-phenyl-furan-3-carbonyl)-amino]-methyl}-benzoic acid (20);
2-Methyl-5-phenyl-furan-3-carboxylic acid [4-(2-benzenesulfonylamino-2-oxo-ethyl)-phenyl]-amide (21);
5-(4-Methoxy-phenyl)-2-trifluoromethyl-furan-3-carboxylic
20 acid [4-(2-benzenesulfonylamino-2-oxo-ethyl)-phenyl]-amide
(22);
5-(4-Methoxy-phenyl)-2-methyl-furan-3-carboxylic acid [4-(2-benzenesulfonylamino-2-oxo-ethyl)-phenyl]-amide (23);
5-Phenyl-furan-3-carboxylic acid {4-[2-oxo-2-(toluene-2-sulfonylamino)-ethyl]-phenyl}-amide
25 (24);
5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic acid [4-(2-benzenesulfonylamino-2-oxo-ethyl)-phenyl]-amide
(25);
5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic
30 acid {4-[2-oxo-2-(toluene-2-sulfonylamino)-ethyl]-phenyl}-amide (26);
5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic acid {4-[2-oxo-2-(propane-1-sulfonylamino)-ethyl]-phenyl}-

amide (27);

5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic acid {4-[2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-2-oxo-ethyl]-phenyl}-amide (28);

5 5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic acid {4-[2-oxo-2-(thiophene-2-sulfonylamino)-ethyl]-phenyl}-amide (29);

5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic acid {4-[2-(5-methyl-pyridine-2-sulfonylamino)-2-oxo-ethyl]-

10 phenyl}-amide (30);

5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic acid [4-(2-oxo-2-phenylmethanesulfonylamino-ethyl)-phenyl]-amide (31);

15 5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic acid {4-[2-oxo-2-(2-trifluoromethyl-benzenesulfonylamino)-ethyl]-phenyl}-amide (32);

5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic acid {4-[2-(4-hydroxy-benzenesulfonylamino)-2-oxo-ethyl]-phenyl}-amide (35); and

20 5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic acid {4-[2-(2-fluoro-benzenesulfonylamino)-2-oxo-ethyl]-phenyl}-amide (36).

The selectivity of the compound for antagonising EP₄ receptors over the other EP receptors (i.e. EP₁, EP₂, EP₃) can be quantified by dividing the Ki for EP₄ (see below) by the Ki for the other EP receptors (see below). The resulting ratio is preferably 10 or more, more preferably 100 or more.

Synthesis Examples

General Experimental Details

All reactions were carried out under an inert atmosphere of nitrogen.

5

Where products were purified by flash chromatography the stationary phase used was silica gel for chromatography, 0.035 to 0.070 mm (220 to 440 mesh) (e.g. Fluka silica gel 60). An applied pressure of nitrogen of ~10 psi was used to accelerate column elution. Thin layer chromatography (TLC) was carried out on aluminium foil plates coated with silica gel containing a fluorescent indicator (254 nm) (e.g. Fluka 60778).

10

15 Petroleum ether refers to that fraction with a boiling point of 40-60°C.

Organic solutions were dried over magnesium sulphate unless otherwise specified.

20

PS-TsCl refers to Polystyrene scavenger resin (loading 1.97 mmol/g) - Argonaut Technologies (P/N 800277)

25 *Preparative HPLC System*

Preparative HPLC was carried out on a C18-reverse-phase column (10 x 2.1 cm i.d Genesis column with 7 µm particle size), eluting with a gradient of acetonitrile (containing 0.1% trifluoroacetic acid) in water (containing 0.1%

30 trifluoroacetic acid) at a flow rate of 5 ml/min. The gradient was started at 50% acetonitrile, and was increased at a rate of 1% per minute up to 90% acetonitrile/water unless otherwise stated. UV detection at 230 nm was used unless otherwise stated.

LC/MS Systems

The Liquid Chromatography Mass Spectroscopy (LC/MS) systems used are as follows..

5 LC/MS System A:

Mass Spectrometer - Platform LC with electrospray source operating in positive and negative ion mode. HP1100 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1100 DAD detection and SEDEX ELS detection.

10

Mobile Phase

- A) Water 0.1 % Formic Acid
- B) acetonitrile 0.1% Formic Acid

15

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.50	2.0	5	95
5.00	2.0	5	95
5.50	2.0	95	5

Column - Luna 3u C18(2) 30x4.6mm

20 LC/MS System B:

Mass Spectrometer - Platform II with electrospray source operating in negative ion mode. HP1100 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1100 DAD detection and SEDEX ELS detection.

25

Mobile Phase

- A) Water 0.1 % Diethylamine
B) acetonitrile

5

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.00	2.0	5	95
4.50	2.0	5	95
5.00	2.0	95	5
20.00	2.0	95	5

Column - XTerra MS C18 3.5µm 4.6 x 30mm

LCMS System C:

10

Mass Spectrometer - Finnigan TSQ700 with electrospray source operating in negative ion mode.
HP1050 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1050 Single wavelength UV detector at 254 nm.

15

Mobile Phase

- A) Water 0.1 % Diethylamine
B) acetonitrile

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
1.00	2.0	95	5
15.00	2.0	5	95
17.00	2.0	5	95

18.00	2.0	95	5
20.00	2.0	95	5

Column - XTerra MS C18 3.5 μ m 4.6 x 30mm

LC/MS System D:

5 Mass Spectrometer - Finnigan TSQ700 with electrospray source operating in positive or negative ion mode.
HP1050 system running at 2.0 mL/min, 200 μ L/min split to the ESI source with inline HP1050 Single Wavelength UV detector at 254 nm.

10

Mobile Phase

- A) Water 0.1 % formic Acid
B) acetonitrile 0.1% formic Acid

15

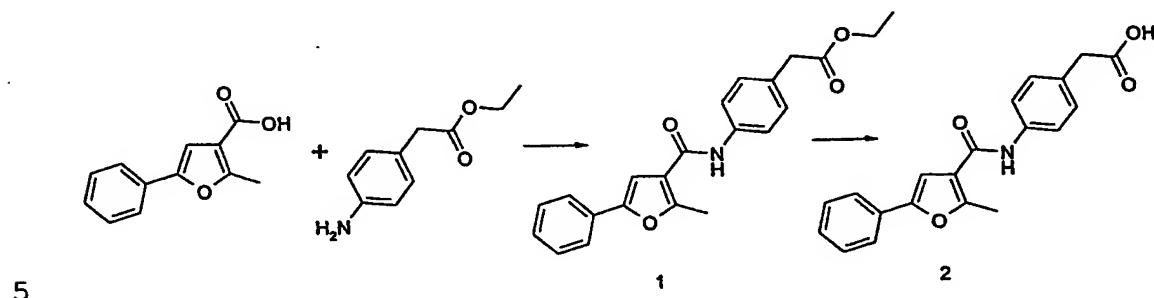
Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
1.00	2.0	95	5
15.00	2.0	5	95
17.00	2.0	5	95
18.00	2.0	95	5
20.00	2.0	95	5

Column - Higgins Clipius C18 5 μ m 100 x 3.0mm

Example 1: Synthesis of [(alkyl-phenyl-furan-3-carbonyl)-amino]-phenyl-acetic acids

(a) {4-[{(2-Methyl-5-phenyl-furan-3-carbonyl)-amino}-phenyl]-acetic acid (2)}



(i) Diisopropylethylamine (427mg) was added to a stirred solution of 2-methyl-5-phenyl-furan-3-carboxylic acid (334mg, 1.6 mmol) and ethyl-4-aminophenyl acetate (296 mg, 1.65mmoles) in N,N-dimethylformamide (30 ml). O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (628mg, 1.65mmoles) was added and the solution was stirred at room temperature for 18 hours. The solvent was evaporated, the residue was dissolved in dichloromethane and washed with water, 10% aqueous sodium carbonate, 1M aqueous hydrochloric acid and finally dried (MgSO_4). After evaporation of the solvent, the residue was triturated with cyclohexane and dried to afford {4-[{(2-Methyl-5-phenyl-furan-3-carbonyl)-amino}-phenyl]-acetic acid ethyl ester (1) (466 mg) as a gum. LC/MS System D; $R_t = 10.64\text{mins}$, $m/z (\text{ES}^+) = 364$ ($\text{M}+\text{H}$ for $\text{C}_{22}\text{H}_{21}\text{NO}_4$).

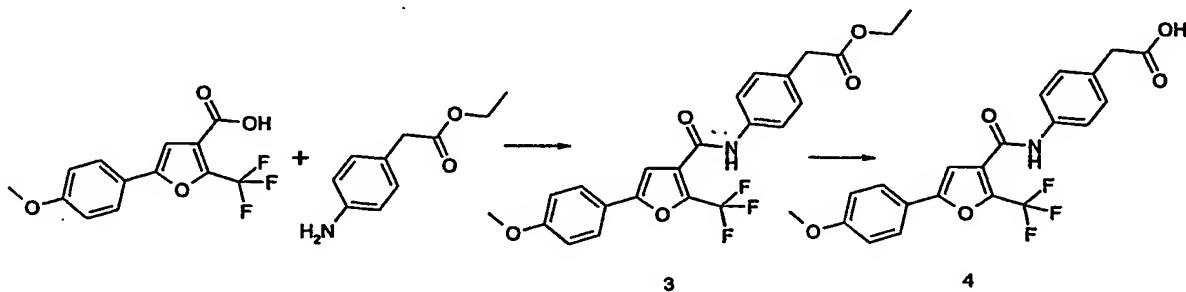
(ii) A solution of sodium hydroxide (150mg) in water (5ml) was added to a stirred solution of {4-[{(2-methyl-5-phenyl-furan-3-carbonyl)-amino}-phenyl]-acetic acid ethyl ester (1) (150mg, 0.41mmoles) in ethanol (20ml) and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated and the residue was diluted with water (10ml) and

acidified to pH2 with 1M aqueous hydrochloric acid. The precipitate was collected, washed with water and the residue was triturated with cyclohexane. Recrystallisation from isopropanol afforded compound (2) (135mg) as a white solid.

- 5 LC/MS System C; $R_t = 4.06\text{mins}$, $m/z (\text{ES}^-) = 334$ ($\text{M}-\text{H}$ for $\text{C}_{20}\text{H}_{17}\text{NO}_4$) .

(b) *(4-{[5-(4-Methoxy-phenyl)-2-trifluoromethyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid (4)*

10

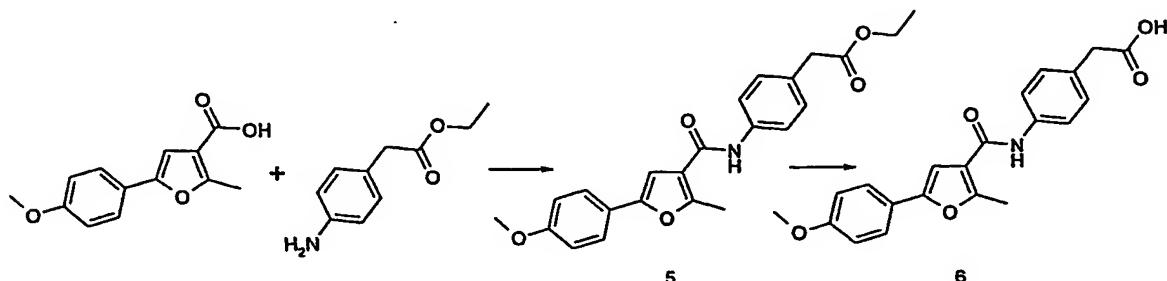


- (i) In an analogous manner to example 1(a)(i), *(4-{[5-(4-Methoxy-phenyl)-2-trifluoromethyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid ethyl ester (3)* was synthesised from 5-(4-methoxy-phenyl)-2-trifluoromethyl-furan-3-carboxylic acid (160mg, 0.56mmol) and ethyl 4-aminophenyl acetate (100mg, 0.56mmoles). 190mg of the product was obtained as a gum.
- 15 LC/MS System A; $R_t = 4.15\text{mins}$, $m/z (\text{ES}^+) = 448$ ($\text{M}+\text{H}$ for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{NO}_5$) .

- (ii) In an analogous manner to example 1(a)(ii), compound (4), was synthesised from *(4-{[5-(4-methoxy-phenyl)-2-trifluoromethyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid ethyl ester (3)* (180mg, 0.403mmoles). The resulting precipitate was collected, washed with water and the residue was triturated with cyclohexane to afford compound

(4) (140mg) as a white solid. LC/MS System D; $R_t = 8.07\text{mins}$,
 $m/z (\text{ES}^+) = 420$ ($\text{M}+\text{H}$ for $\text{C}_{21}\text{H}_{16}\text{F}_3\text{NO}_5$).

(c) (4-{[5-(4-Methoxy-phenyl)-2-methyl-furan-3-carbonyl]-5-amino}-phenyl)-acetic acid (6)

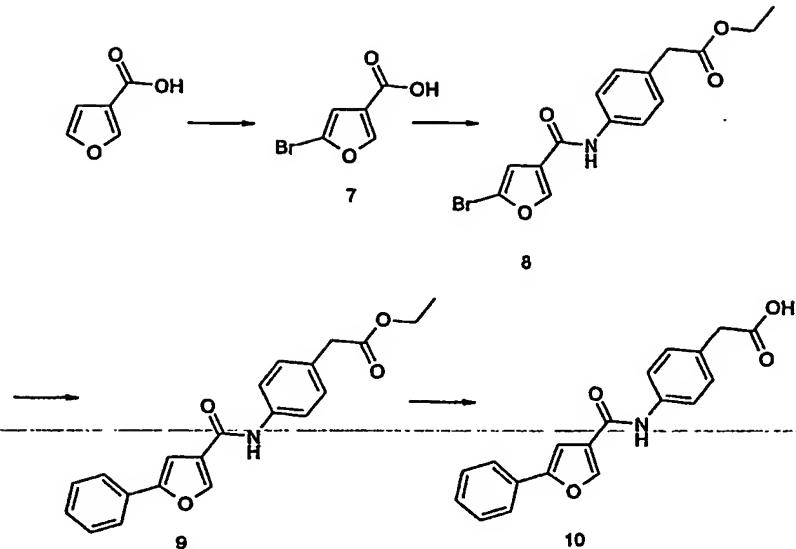


(i) In an analogous manner to example 1(a)(i), (4-{[5-(4-Methoxy-phenyl)-2-methyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid ethyl ester (5) was synthesised from 5-(4-methoxy-phenyl)-2-methyl-furan-2-carboxylic acid (250mg, 1.077mmol) and ethyl-4-aminophenyl acetate (193mg, 1.077mmoles). 80mg of the compound was obtained as a gum. LC/MS System A; $R_t = 4.03\text{mins}$, $m/z (\text{ES}^+) = 394$ ($\text{M}+\text{H}$ for $\text{C}_{23}\text{H}_{23}\text{NO}_5$).

15

(ii) In an analogous manner to example 1(a)(ii), compound (6), was synthesised from {4-[{(5-phenyl-furan-3-carbonyl)-amino}-phenyl]-acetic acid ethyl ester (5) (50mg, 0.143mmoles). The resulting precipitate was collected, 20 washed with water and the residue was triturated with cyclohexane to afford compound (6) (14mg) as a white solid. LC/MS System D; $R_t = 7.25\text{mins}$, $m/z (\text{ES}^+) = 322$ ($\text{M}+\text{H}$ for $\text{C}_{19}\text{H}_{15}\text{NO}_4$).

25 (d) {4-[{(5-Phenyl-furan-3-carbonyl)-amino}-phenyl]-acetic acid (10)}



(i) To a stirred solution of pyridinium tribromide (14.3g, 44.6mmoles) in acetic acid (20 ml) was added 3-furoic acid (5g, 44.6mmoles). The resulting mixture was heated at 40°C for 16 hours. The acetic acid was evaporated; the residue was dissolved in dichloromethane (50ml), washed with water (3x50ml) and dried (MgSO_4). The solvent was evaporated and the residue was purified by HPLC (gradient: 20% acetonitrile/80% water containing 0.1% trifluoroacetic acid to 80% acetonitrile/20% water at a rate of 1%/min) to afford 5-Bromo-furan-3-carboxylic acid (7) as a white solid. LC/MS System A; $R_t = 2.52\text{mins}$, $m/z (\text{ES}^-) = 189/191$ ($M-\text{H}$ for $\text{C}_5\text{H}_3\text{BrO}_3$).

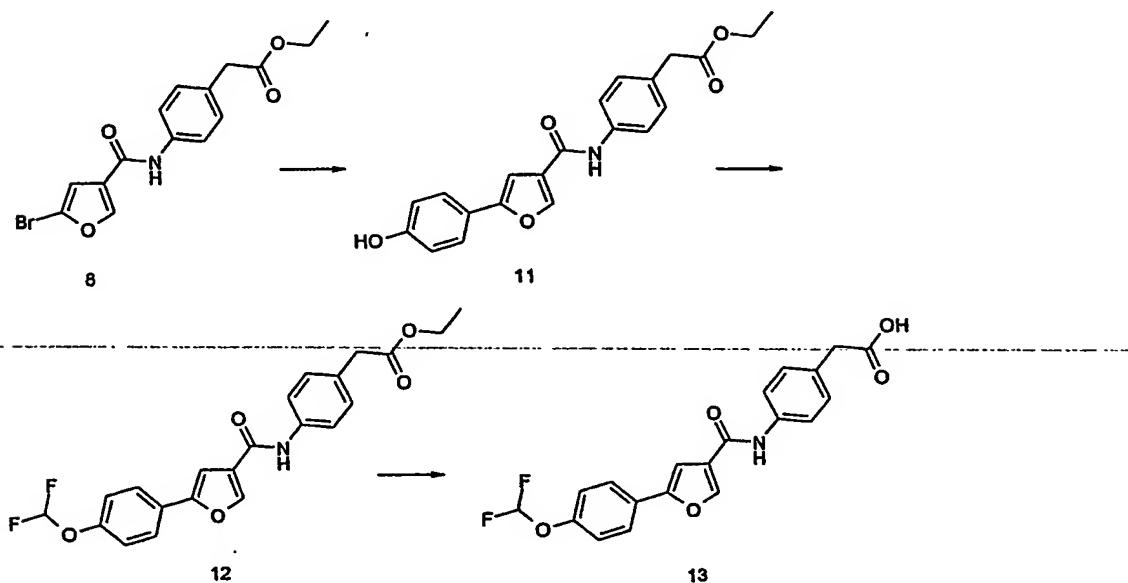
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(ii) In an analogous manner to example 1(a)(i), {4-[$(5-$ bromo-furan-3-carbonyl)-amino]-phenyl}-acetic acid ethyl ester (8) was synthesised from 5-bromo-furan-3-carboxylic acid (7) (225mg, 1.18mmol) and ethyl-4-aminophenyl acetate (213mg, 1.18mmoles). 403mg of the product was obtained as a brown solid. LC/MS System A; $R_t = 3.49\text{mins}$, $m/z (\text{ES}^+) = 352/354$ ($M+\text{H}$ for $\text{C}_{15}\text{H}_{14}\text{BrNO}_4$).

(iii) A solution of {4-[(5-bromo-furan-3-carbonyl)-amino]-phenyl}-acetic acid ethyl ester (**8**) (200mg, 0.57mmoles), phenyl boronic acid (69.2mg, 0.57 mmoles), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (50mg, 5 0.06mmoles) and 2M aqueous cesium carbonate (1.2ml, 2.4mmoles) in toluene (20ml) was refluxed for 16 hours. The solvent was evaporated, the residue diluted with water (20ml) and then extracted with ethyl acetate (3x20ml). The combined organic layers were concentrated *in vacuo*. The 10 residue was purified by flash chromatography (gradient elution with 90% cyclohexane / 10% ethyl acetate to 50%cyclohexane / 50%ethyl acetate) to afford {4-[(5-phenyl-furan-3-carbonyl)-amino]-phenyl}-acetic acid ethyl ester (**9**) (53mg). LC/MS System A; R_t = 3.84mins, m/z (ES⁺) = (M+H 15 for C₂₁H₁₉NO₄).

(iv) In an analagous manner to example 1(a)(ii), compound (**10**), was synthesised from {4-[(5-phenyl-furan-3-carbonyl)-amino]-phenyl}-acetic acid ethyl ester (**9**) (50mg, 20 0.143mmoles). The resulting precipitate was collected, washed with water and the residue was triturated with cyclohexane to afford compound (**10**) (14mg) as a white solid. LC/MS System D; R_t = 7.25mins, m/z (ES⁺) = 322 (M+H for C₁₉H₁₅NO₄).

(e) (4-((5-(4-Difluoromethoxy-phenyl)-furan-3-carbonyl)-amino)-phenyl)-acetic acid (13)



(i) A solution of {4-[(5-Bromo-furan-3-carbonyl)-amino]-phenyl}-acetic acid ethyl ester (828mg, 2.35mmoles) (8), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (518mg, 2.35 mmoles), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (50mg) and 2M aqueous cesium carbonate (3.5ml, 3.5mmoles) in N,N-dimethylformamide (20ml) was heated in a microwave reactor at 100°C for 15 minutes. The solvent was evaporated, and the residue was purified by flash chromatography (gradient elution with 100% cyclohexane to 50%cyclohexane / 50% ethyl acetate) to afford (4-((5-(4-hydroxy-phenyl)-furan-3-carbonyl)-amino)-phenyl)-acetic acid ethyl ester (11) (328mg). LC/MS System A; R_t = 3.35mins, m/z (ES⁺) = 366 (M+H for $C_{21}H_{19}NO_5$).

(ii) To a stirred solution of (4-((5-(4-hydroxy-phenyl)-furan-3-carbonyl)-amino)-phenyl)-acetic acid ethyl ester (328mg, 0.898mmoles) (11) in N,N-dimethylformamide (15ml) was added potassium carbonate (190mg, 1.35 mmoles) and

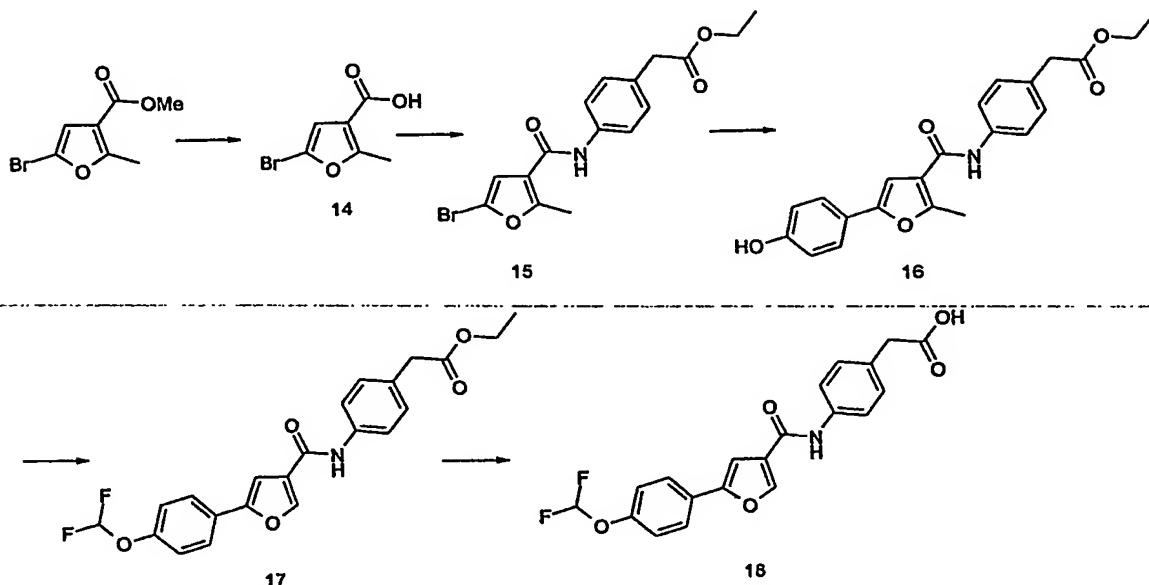
potassium iodide (75mg, 0.449mmoles). Chlorodifluoromethane was bubbled through the solution at 80°C for 5 hours, and then discontinued. The reaction mixture was stirred at 80°C for 16 hours. The reaction was cooled to room temperature 5 and quenched by the addition of water until no effervescence was observed. The resulting solution was extracted with ethyl acetate and the combined organic layers washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient: 100% 10 cyclohexane to 50% cyclohexane / 50% ethyl acetate) to afford (4-{{[5-(4-Difluoromethoxy-phenyl)-furan-3-carbonyl]-amino}-phenyl}-acetic acid ethyl ester (**12**) (60mg) as a yellow solid. LC/MS System A; R_t = 3.91mins, m/z (ES⁺) = 416 (M+H for C₂₂H₁₉F₂NO₅).

15

(iii) In an analogous manner to example 1(a)(ii), compound (**13**), was synthesised from (4-{{[5-(4-difluoromethoxy-phenyl)-furan-3-carbonyl]-amino}-phenyl}-acetic acid ethyl ester (**12**) (55mg, 0.132 mmoles). The resulting precipitate 20 was collected, washed with water and the residue was triturated with cyclohexane to afford the compound (**13**) (41.8mg) as a white solid. LC/MS System D; R_t = 8.86mins, m/z (ES⁺) = 388 (M+H for C₂H₁₅ F₂NO₅).

25

(f) (4-{[5-(4-Difluoromethoxy-phenyl)-furan-3-carbonyl]-amino}-phenyl)-acetic acid (18)



5 (i) A solution of sodium hydroxide (4.5g) in water (10ml) was added to a stirred solution of 5-bromo-2-methyl-furan-3-carboxylic acid methyl ester (5g, 23mmoles) in methanol (70ml) and the mixture was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was
10 diluted with water (10ml) and acidified to pH2 with 1M aqueous hydrochloric acid. The precipitate was collected, washed with water, dried at 40°C to afford 5-Bromo-2-methyl-furan-3-carboxylic acid (14) (4g). LC/MS System A; R_t = 2.86min.

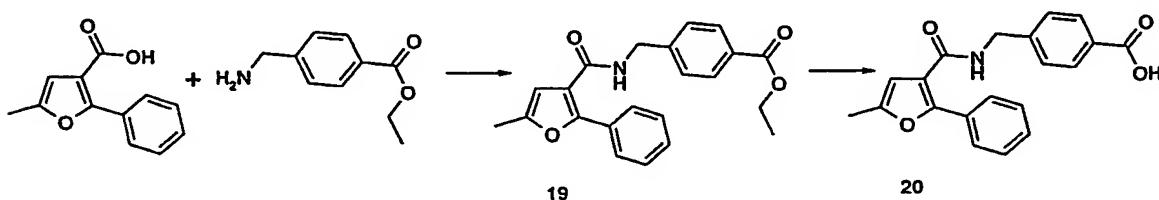
15 (ii) In an analogous manner to example 1(a)(i), {4-[{(5-bromo-2-methyl-furan-3-carbonyl)-amino}-phenyl]-acetic acid ethyl ester (15) was synthesised from 5-bromo-2-methyl-furan-3-carboxylic acid (14) (1.8g, 8.78mmoles) and (4-amino-phenyl)-acetic acid etyl ester(1.6g, 8.9mmoles). 3.08g of the product was obtained as a gum. LC/MS System A; R_t = 3.73mins, m/z (ES⁺) = 367 (M+H for C₁₆H₁₆BrNO₄).

(iii) A solution of {4-[(5-bromo-2-methyl-furan-3-carbonyl)-amino]-phenyl}-acetic acid ethyl ester (3g, 8.19mmoles) (15), 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-5 phenol (1.8g, 8.19 mmoles), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (300mg, 10%) and 2M aqueous cesium carbonate (15ml, 15mmoles) in N,N-dimethylformamide (35ml) was heated in a microwave reactor at 100°C for 15 minutes. The solvent was evaporated, 10 and the residue was purified by flash chromatography (gradient elution with 100% cyclohexane to 100% ethyl acetate) to afford (4-{[5-(4-hydroxy-phenyl)-2-methyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid ethyl ester (16) (1.9g). LC/MS System A; R_t = 3.54mins, m/z (ES⁺) = 380
15 (M+H for C₂₂H₂₁NO₅).

(iv) To a stirred solution of (4-{[5-(4-hydroxy-phenyl)-2-methyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid ethyl ester (1.9g, 5mmoles) (16) in N, N-dimethylformamide (70ml) 20 was added potassium carbonate (1.04g, 7.5 mmoles) and potassium iodide (416m g, 2.5mmoles). Chlorodifluoromethane was bubbled through the solution at 80°C for 5 hours, and then discontinued. The reaction mixture was stirred at 80°C for 16 hours. The reaction was cooled to room temperature 25 and quenched by the addition of water until no effervescence was observed. The resulting solution was extracted with ethyl acetate (3x150ml) and the combined organic layers washed with brine (200ml), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography 30 (gradient: 100% cyclohexane to 50% cyclohexane / 50% ethyl acetate) to afford (4-{[5-(4-difluoromethoxy-phenyl)-2-methyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid ethyl ester (17) (694mg) as a white solid. LC/MS System A; R_t = 4.13mins, m/z (ES⁺) = 430 (M+H for C₂₃H₂₁F₂NO₅).

(v) In an analogous manner to example 1(a)(ii), compound (18), was synthesised from (4-[(5-(4-difluoromethoxy-phenyl)-2-methyl-furan-3-carbonyl]-amino)-phenyl)-acetic acid ethyl ester (17) (694mg, 1.62 mmoles). The resulting precipitate was collected, washed with water and the residue was triturated with cyclohexane to afford compound (18) (643mg) as a white solid. LC/MS System D; $R_t = 9.46\text{mins}$, m/z (ES^+) = 402 ($\text{M}+\text{H}$ for $\text{C}_{21}\text{H}_{17}\text{F}_2\text{NO}_5$).

Example 2: Synthesis of 4-{{[(5-Methyl-2-phenyl-furan-3-carbonyl)-amino]-methyl}-benzoic acid (20)}

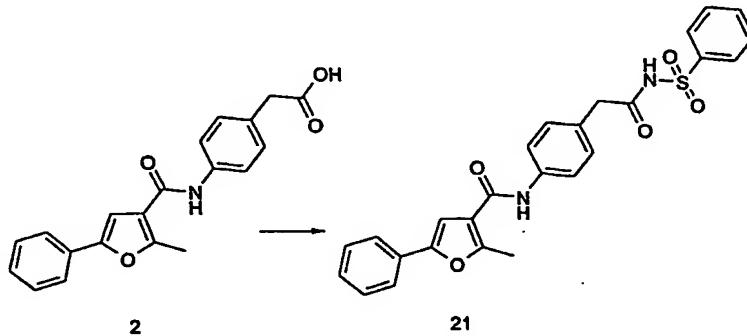


15 (i) In an analogous manner to example 1(a)(i), 4-{{[5-methyl-2-phenyl-furan-3-carbonyl]-amino}-methyl}-benzoic acid ethyl ester (**19**) was synthesised from 5-methyl-2-phenyl-furan-3-carboxylic acid (79mg, 0.39mmol) and 4-aminomethyl benzoic acid ethyl ester (70mg, 0.39mmoles).
 20 99mg of the product was obtained as a gum. LC/MS System A;
 $R_t = 3.88\text{mins}$, $m/z (\text{ES}^+) = 364$ ($\text{M}+\text{H}$ for $\text{C}_{22}\text{H}_{21}\text{NO}_4$).

(ii) In an analogous manner to example 1(a)(ii), compound (20), was synthesised from 4-{{(5-methyl-2-phenyl-furan-3-carbonyl)-amino}-methyl}-benzoic acid ethyl ester (19) (90mg, 0.247mmoles). The resulting precipitate was collected, washed with water and the residue was triturated with cyclohexane to afford compound (20) (51mg) as a white solid. LC/MS System D; R_t = 6.82mins, m/z (ES⁺) = 336 (M+H for $C_{20}H_{17}NO_4$).

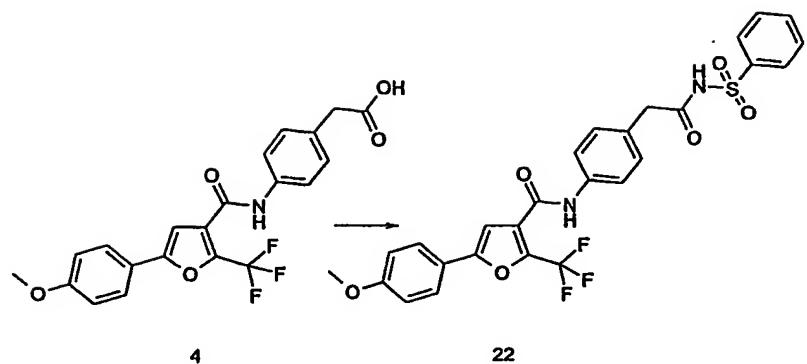
**Example 3: Synthesis of alkyl-phenyl-furan-3-carboxylic acid
[4-(2-sulphonylamino-2-oxo-ethyl)-phenyl] amides**

- 5 (a) *2-Methyl-5-phenyl-furan-3-carboxylic acid [4-(2-benzenesulfonylamino-2-oxo-ethyl)-phenyl]-amide (21)*



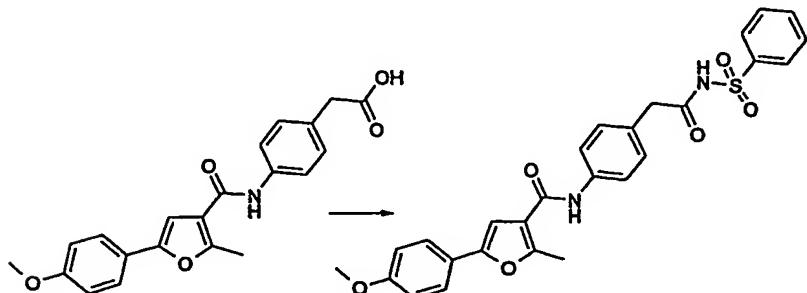
A stirred solution of {4-[{(2-methyl-5-phenyl-furan-3-carbonyl)-amino}-phenyl]-acetic acid (2) (10mg, 10 0.030mmoles), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.7mg, 0.030mmoles), and 4-(N, N-dimethylamino)-pyridine (3.5mg) in dichloromethane (10ml), was treated with benzenesulphonamide (9mg, 0.060mmoles). The mixture was stirred at room temperature for 18 hours. The 15 reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate, washed with 0.1M aqueous hydrochloric acid, and brine and finally dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by HPLC (gradient: 20% acetonitrile/80% water containing 20 0.1% trifluoroacetic acid to 80% acetonitrile/20% water at a rate of 1%/min) to afford compound (21) (10mg) as a white solid. LC/MS System D; R_t = 9.98mins, m/z (ES^+) = 475 ($M+H$ for $C_{26}H_{22}N_2O_5S$).

- 25 (b) *5-(4-Methoxy-phenyl)-2-trifluoromethyl-furan-3-carboxylic acid [4-(2-benzenesulfonylamino-2-oxo-ethyl)-phenyl]-amide (22)*



In an analogous way to example 3-(a), compound (22) was synthesised from (4-{[5-(4-methoxy-phenyl)-2-trifluoromethyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid (4) (40mg, 0.095mmoles). The reaction mixture was concentrated *in vacuo* and the residue was dissolved in dichloromethane, washed with 0.1M aqueous hydrochloric acid, and brine and finally dried (MgSO_4). After evaporation of the solvent, the residue was triturated with cyclohexane and a white solid filtered off, which was purified by HPLC (gradient: 20% acetonitrile/80% water containing 0.1% trifluoroacetic acid to 80% acetonitrile/20% water at a rate of 1%/min) to afford compound (22) (12mg) as a white solid. LC/MS System D; $R_t = 9.08\text{mins}$, $m/z (\text{ES}^+) = 559$ ($\text{M}+\text{H}$ for $\text{C}_{27}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_6\text{S}$).

(c) 5-(4-Methoxy-phenyl)-2-methyl-furan-3-carboxylic acid [4-(2-benzenesulfonylamino-2-oxo-ethyl)-phenyl]-amide (23)

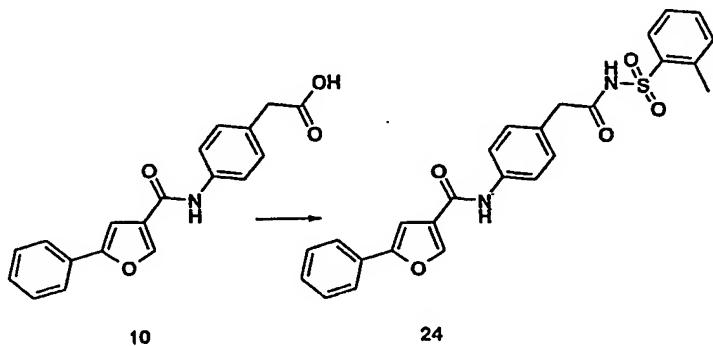


In an analogous way to example 3(a), compound (23) was synthesised from (4-{[5-(4-methoxy-phenyl)-2-methyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid (6) (100mg,

5 0.273mmoles). The reaction mixture was concentrated in
vacuo and the residue was dissolved in dichloromethane,
washed with 0.1M aqueous hydrochloric acid, and brine and
finally dried ($MgSO_4$). After evaporation of the solvent, the
residue was triturated with cyclohexane and a white solid
10 filtered off, which was then purified by HPLC (gradient: 20%
acetonitrile/80% water containing 0.1% trifluoroacetic acid
to 80% acetonitrile/20% water at a rate of 1%/min) to afford
compound (23) (50mg) as a white solid. LC/MS System D; R_t =
8.58mins, m/z (ES^+) = 405 ($M+H$ for $C_{27}H_{24}N_2O_6S$).

15

(d) 5-Phenyl-furan-3-carboxylic acid {4-[2-oxo-2-(toluene-2-sulfonylamino)-ethyl]-phenyl}-amide (24)

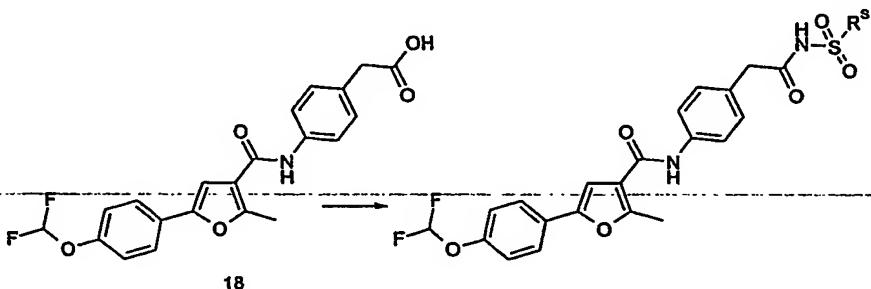


In an analogous way to example 3(a), compound (24) was synthesised from {4-[(5-phenyl-furan-3-carbonyl)-amino]-phenyl}-acetic acid (10) (40mg, 0.125mmoles) and replacing benzene-sulfonamide with toluene-2-sulfonamide. The reaction mixture was concentrated *in vacuo* and the residue purified by HPLC (gradient: 20% acetonitrile/80% water containing 0.1% trifluoroacetic acid to 80% acetonitrile/20% water at a rate of 1%/min) to afford compound (24) (4mg) as an off-white solid. LC/MS System D; R_t = 9.85mins, m/z (ES⁺)

= 475 (M+H for C₂₆H₂₂N₂O₅S).

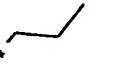
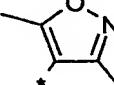
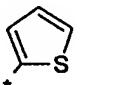
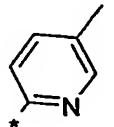
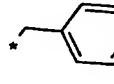
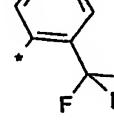
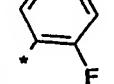
(e) Compounds derived from (4-[[5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carbonyl]-amino]-phenyl)-acetic acid (18)

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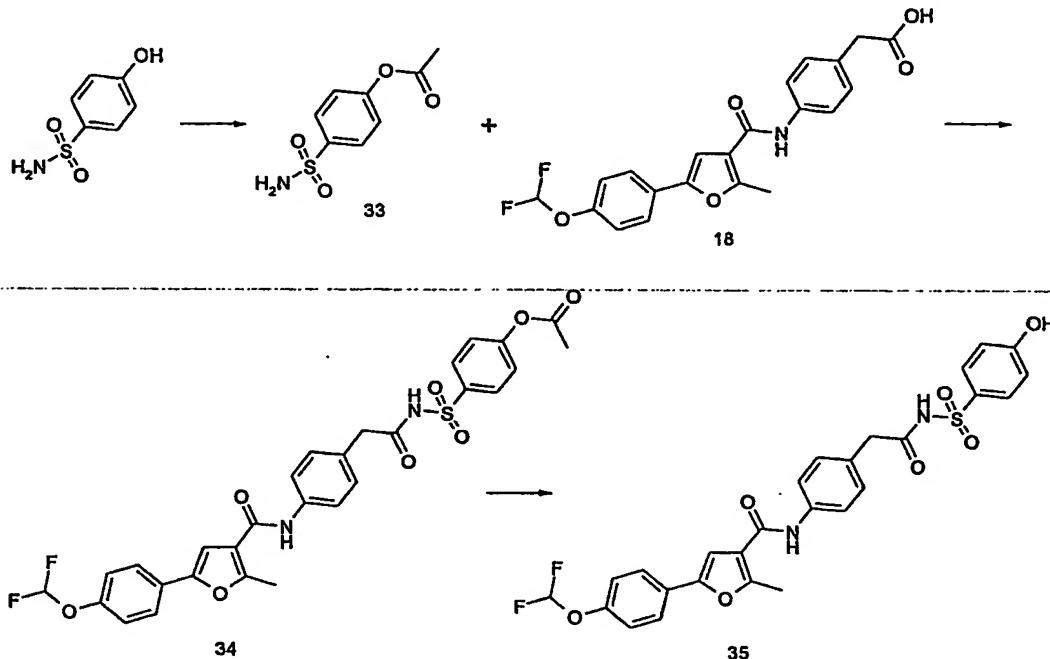


A stirred solution of (4-[[5-(4-difluoromethoxy-phenyl)-2-methyl-furan-3-carbonyl]-amino]-phenyl)-acetic acid (18) (20mg, 0.050mmoles), 1-(3-dimethylaminopropyl)-3-10 ethylcarbodiimide hydrochloride (19.1mg, 0.010mmoles), and 4-(N,N-dimethylamino)-pyridine (6mg, 0.050mmoles) in dichloromethane (10ml), was treated with a sulphonamide (R^sS(=O)₂NH₂) (0.055mmoles). The mixture was stirred at room temperature for 1.5 hours (compounds 25 and 26), 2 hours 15 (compound 31) or 16 hours (compounds 27 to 30, 32 and 36). The reaction mixture was concentrated *in vacuo* and the residue purified by HPLC (gradient: 20% acetonitrile/80% water containing 0.1% trifluoroacetic acid to 80% acetonitrile/20% water at a rate of 1%/min) to afford the 20 desired compound.

Compound	R ^s	Yield (mg)	LC/MS R _t (mins) System D	m/z (ES ⁻)
25		20	10.51	539
26		12	10.79	553

27		12.5	9.98	505
28		37.8	10.38	558
29		33	10.22	545
30		45	9.87	554
31		38	10.57	553
32		42.8	10.78	607
36		60	10.32	557

(f) 5-(4-Difluoromethoxy-phenyl)-2-methyl-furan-3-carboxylic acid {4-[2-(4-hydroxy-benzenesulfonylamino)-2-oxo-ethyl]-phenyl}-amide (35)



- 5 (i) A solution of sodium hydroxide (116mg, 2.9mmoles) in water (10ml) was added to a stirred solution of 4-hydroxybenzenesulphonamide (500mg, 2.9mmoles) in water (30 ml). This mixture was treated with acetic anhydride (295mg, 2.9mmoles) and stirred at room temperature for 4.5 hours.
- 10 The reaction mixture was filtered off and the resulting solid washed with water to afford acetic acid 4-sulphamoyl-phenyl ester (33) (348mg) as a yellow solid. LC/MS System A; R_t 2.06mins.
- 15 (ii) In an analogous way to example 3(e), (4-{[5-(4-difluoromethoxy-phenyl)-2-methyl-furan-3-carbonyl]-amino}-phenyl)-acetic acid (18) (50mg, 0.125mmoles) was treated with acetic acid 4-sulphamoyl-phenyl ester (33) (29.2mg, 0.137mmoles). The mixture was stirred at room temperature
- 20 for 16 hours. The reaction mixture was concentrated and the product (34) used as described in step (iii) without further

purification. LC/MS System A; R_t 3.89mins, m/z (ES⁺) = 599
(M+H for $C_{29}H_{24}F_2N_2O_8S$).

(iii) Sodium methoxide (6.8mg, 0.125mmoles) and water (1ml).
5 were added to a stirred solution of acetic acid 4-[2-(4-{[5-(4-difluoromethoxy-phenyl)-2-methyl-furan-3-carbonyl]-amino}-phenyl)-acetylsulphamoyl]-phenyl ester (34) (74.5mg, 0.125mmoles) in methanol (10ml). The reaction mixture was stirred at room temperature for 30 minutes, concentrated and 10 the residue was purified by HPLC (gradient: 20% acetonitrile/80% water containing 0.1% trifluoroacetic acid to 80% acetonitrile/20% water at a rate of 1%/min) to afford compound (35) (18mg) as a white solid. LC/MS System D; R_t = 9.48mins, m/z (ES⁻) = 555 (M-H for $C_{27}H_{22}F_2N_2O_7S$).

15

Example 4: Biological Results

Binding ability to human EP receptors

Membranes were prepared from cells stably transfected with 20 human EP receptor cDNA. In brief, cells were cultured to confluence, scraped from culture flasks, and centrifuged (800 g, 8 minutes, 4°C). Cells were twice washed in ice cold homogenisation buffer containing 10 mMTris-HCl, 1 mM EDTA.2Na, 250 mM sucrose, 1 mM PMSF, 0.3 mM indomethacin, pH 7.4, homogenised and re-centrifuged as before. The 25 supernatant was stored on ice and pellets re-homogenised and re-spun. Supernatants were pooled and centrifuged at 40000g, 10 minutes, 4°C. Resultant membrane pellets were stored at -80°C until use.

30 For assay, membranes expressing human EP₄, EP₃, EP₂ or EP₁ receptors were incubated in Millipore (MHVBN45) plates containing assay buffer, radiolabelled [³H]PGE₂ and 0.1 to 10 000 nM concentrations of compounds. Incubations were

performed at suitable temperatures and for suitable times to allow equilibrium to be reached. Non-specific binding was determined in the presence of 10uM PGE₂. Bound and free radiolabel was separated by vacuum manifold filtration using appropriate wash buffers, and bound radiolabel was determined by scintillation counting. Constituents of each of the buffers are included in table 1 below.

The affinity or pK_i of each compound for each receptor was calculated from the concentration causing 50% radioligand displacement (IC₅₀) using the Cheng-Prusoff equation:

$$Ki = \frac{IC_{50}}{1 + \left(\frac{\text{radioligand concentration}}{\text{radioligand } KD} \right)}$$

This approach follows that set out in Kenakin, T.P., Pharmacologic analysis of drug receptor interaction. Raven Press, New York, 2nd edition.

Table 1

Receptor		EP ₁	EP ₂	EP ₃	EP ₄
Protein / well		6.5μg	8μg	5μg	5μg
Final [³ H-PGE ₂]		3.6nM	3nM	2.5nM	1nM
Buffer	Assay	10mM MES pH6.0; 10mM MES pH6.0; 10mM MgCl ₂ ; 1mM EDTA, 3uM Indomethacin	10mM MES pH6.0; 10mM MgCl ₂ ; 1mM EDTA	10mM MES pH6.0; 10mM MgCl ₂ ; 1mM EDTA, 100uM GTP-gamma-S	10mM MES pH6.0; 10mM MgCl ₂ ; 1mM EDTA, 3uM Indomethacin
	Wash	10mM MES pH6.0; 10mM MgCl ₂	10mM MES pH6.0; 10mM MgCl ₂	10mM MES pH6.0; 10mM MgCl ₂	10mM MES pH6.0; 1mM EDTA

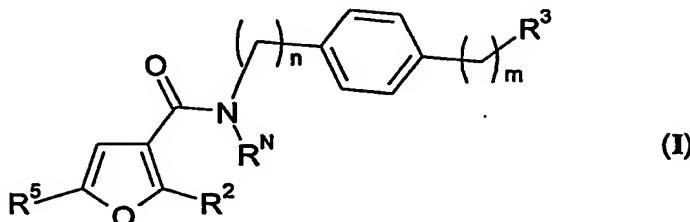
The results are presented as pK_i values in table 2 below.

Table 2

Compound	EP ₄	EP ₂	EP ₃
4	>5	<5	<5
6	>6	<5	<5
10	>6	<5.5	<5
13	>6	<5	<5
18	>6	<5.5	<5
20	>5	<5	<5
21	>7	<6	<5
22	>6	<6	<5
23	>7	<6	<5
24	>6	<7	<5
25	>7	<6	<5
26	>7	<6.5	<5
27	>6	<5	<5
28	>6	<5	<5
29	>7	<5.5	<5
30	>7	<6	<5
31	>7	<6	<5
32	>7	<5.5	<5.5
35	>7	<5.5	<5
36	>7	<6	<5

CLAIMS:

1. A compound of formula (I):



5 or a salt, solvate and chemically protected form thereof,
wherein:

one of R² and R⁵ is:

(i) H or an optionally substituted C₁₋₄ alkyl group; or

(ii) an optionally substituted C₅₋₇ aryl; and the other of R²

10 and R⁵ is the other group;

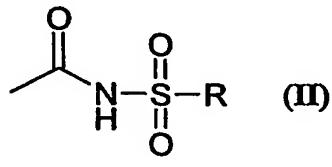
m and n can be 0 or 1, and m + n = 1 or 2

R^N is H or optionally substituted C₁₋₄ alkyl

R³ is either:

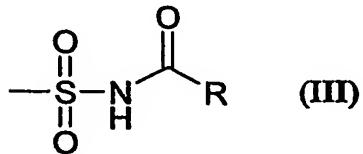
(i) carboxy;

15 (ii) a group of formula (II):



;

(iii) a group of formula (III):



20 wherein R is optionally substituted C₁₋₇ alkyl, C₅₋₂₀ aryl, or
NR^{N3}R^{N4}, where R^{N3} and R^{N4} are independently selected from
optionally substituted C₁₋₄ alkyl; or
(iv) tetrazol-5-yl.

2. A compound according to claim 1, wherein R⁵ is the

optionally substituted C₅₋₇ aryl group and R² is H or the optionally substituted C₁₋₄ alkyl group.

3. A compound according to claim 2, wherein R² is selected
5 from H or an optionally substituted C₁₋₃ alkyl group.

4. A compound according to claim 3, wherein R² is a methyl group.

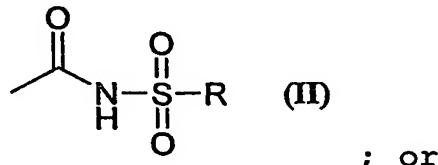
10 5. A compound according to any one of claims 2 to 4,
wherein R⁵ is a C₆ aryl group.

6. A compound according to claim 5, wherein R⁵ is preferably phenyl.

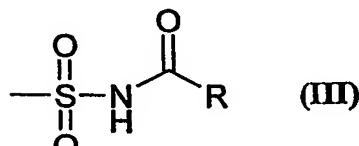
15 7. A compound according to any one of the preceding claims wherein the C₅₋ aryl group is substituted by substituents selected from C₁₋₇ alkoxy groups.

20 8. A compound according to any one of the preceding claims wherein R³ is either:

(i) a group of formula (II):



(ii) a group of formula (III):



25

9. A compound according to claim 8, wherein R is selected from an optionally substituted C₅₋₂₀ aryl group, and an

optionally substituted C₅₋₂₀ aryl-C₁₋₇ alkyl group.

10. A compound according to claim 8, wherein R is a C₁₋₇ alkyl group.

5

11. A compound according to any one of the preceding claims, wherein n + m = 1.

12. A compound according to claim 11, wherein n is 0 and m
10 is 1.

13. A compound according to any one of the preceding claims, wherein R^N is H or methyl.

15 14. The use of a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof in a method of therapy.

20 15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

25 16. The use of a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by antagonism of an EP₄ receptor.

30 17. The use according to claim 16, wherein the condition which can be alleviated by antagonism of an EP₄ receptor is a primary headache disorder.

18. The use according to claim 17, wherein the primary headache disorder is a migraine.

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